STABLE LAMOTRIGINE PHARMACEUTICAL COMPOSITIONS AND PROCESSES FOR THEIR PREPARATION

Technical Field of the Invention

The present invention relates to a stable pharmaceutical composition of lamotrigine and pharmaceutically acceptable acid addition salts thereof. The invention also relates to a process for the preparation of such a composition.

Background of the Invention

Lamotrigine is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine. Lamotrigine is indicated as adjunctive therapy for the treatment of partial seizures in adults with epilepsy.

U.S. Patent No. 5,861,179 discloses a powder formulation of lamotrigine that includes lamotrigine or a pharmaceutically acceptable acid addition salt thereof with lactose, starch, crystalline cellulose and polyvinylpyrrolidone. Further specified are the specific grades, concentrations and particle size of the excipients, which are necessary to make a stable powder formulation. One specific formulation disclosed is (a) from 0.5 to 50% by weight of lamotrigine or a pharmaceutically acceptable acid addition salt thereof, (b) from 15 to 50% by weight of lactose, (c) from 15 to 50% by weight of starch, (d) from 0.5 to 15% by weight of crystalline cellulose, and (e) from 5 to 15% by weight of polyvinylpyrrolidone. The formulation is further characterized as being in the form of a free-flowing powder of granules in which (i) no granules have a particle size of greater than 850 microns, (ii) at least 90% by weight of the granules have a particle size of from 75 to 850 microns, (iii) the granules disintegrate within 30 minutes according to the Disintegration Test of The Pharmacopoeia of Japan, twelfth edition, 1991, and (iv) at least 90% by weight of the lamotrigine or lamotrigine salt in the granules dissolves within 30 minutes when the granules are subjected to the Dissolution Test, method 2 (paddle method) of The Pharmacopoeia of Japan, twelfth edition, 1991. Also disclosed is the use of spray granulation as a process to make such a powder formulation.

As described in more detail below, the inventors have surprisingly found that stable formulations of lamotrigine can be prepared by a simple process without the stringent particle

size and grade requirements required in U.S. Patent No. 5,861,179. Moreover, the amounts of the excipients present do not need to be within the range disclosed in that patent.

Summary of the Invention

In one general aspect there is provided a pharmaceutical composition that includes:

(a) from about 0.1% to about 50 % by weight of lamotrigine or acid addition salt thereof;

(b) from about 15.5% to about 70% by weight of microcrystalline cellulose;

(c) from about 0.1% to about 14.5% by weight of sodium starch glycolate; and

(d) from about 0.1% to about 4.5% by weight of polyvinylpyrrolidone.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the pharmaceutical composition may further include about 17% to about 70% by weight of microcrystalline cellulose, about 0.1% to about 13% by weight of sodium starch glycolate, and about 0.1% to about 4% by weight of polyvinylpyrrolidone.

The pharmaceutical composition may further include from about 0.1% to about 14.5% by weight of lactose. The pharmaceutical composition may further include about 17% to about 70% by weight of microcrystalline cellulose, about 0.1% to about 13% by weight of sodium starch glycolate, about 0.1% to about 4% by weight of polyvinylpyrrolidone, and about 0.1% to about 13% by weight of lactose. The pharmaceutical composition may still further include about 20% to about 70% by weight of microcrystalline cellulose, about 0.1% to about 10% by weight of sodium starch glycolate, about 0.1% to about 3% by weight of polyvinylpyrrolidone, and about 0.1% to about 10% by weight of lactose.

The sodium starch glycolate may be intragranularand/or extragranular. The pharmaceutical composition may be a tablet.

At least 80% by weight of the lamotrigine or the acid addition salt thereof may dissolve within 10 minutes. At least 90% by weight of the lamotrigine or the acid addition salt thereof may dissolve within 30 minutes.

The pharmaceutical composition may be stable after three months storage at 40°C and 75% RH with at least 98% of the lamotrigine or acid addition salt thereof remaining after three months.

In another general aspect there is provided a process for preparing a pharmaceutical composition. The process includes wet granulating a composition that includes:

(a) from about 0.1% to about 50 % by weight of lamotrigine or acid addition salt thereof;

(b) from about 15.5% to about 70% by weight of microcrystalline cellulose;

(c) from about 0.1% to about 14.5% by weight of sodium starch glycolate; and

(d) from about 0.1% to about 4.5% by weight of polyvinylpyrrolidone.

Embodiments of the process may include one or more of the following features. For example, the pharmaceutical composition may further include about 17% to about 70% by weight of microcrystalline cellulose, about 0.1% to about 13% by weight of sodium starch glycolate, and about 0.1% to about 4% by weight of polyvinylpyrrolidone.

The pharmaceutical composition may further include from about 0.1% to about 14.5% by weight of lactose. The pharmaceutical composition may further include about 17% to about 70% by weight of microcrystalline cellulose, about 0.1% to about 13% by weight of sodium starch glycolate, about 0.1% to about 4% by weight of polyvinylpyrrolidone, and about 0.1% to about 13% by weight of lactose. The pharmaceutical composition may still further include about 20% to about 70% by weight of microcrystalline cellulose, about 0.1% to about 10% by weight of sodium starch glycolate, about 0.1% to about 3% by weight of polyvinylpyrrolidone, and about 0.1% to about 10% by weight of lactose.

The lamotrigine or its acid addition salt, microcrystalline cellulose, sodium starch glycolate, polyvinylpyrrolidone and/or lactose may be blended and then granulated with water. The lamotrigine or its acid addition salt, microcrystalline cellulose, sodium starch glycolate and/or lactose may be blended and then granulated with an aqueous solution of polyvinylpyrrolidone.

The process may further include screening the wet mass to obtain granules. The process may still further include drying and sieving the granules. The process may still further include compressing the granules to form tablets.

The sodium starch glycolate may be is intragranular and/or extragranular.

In another general aspect there is provided a method of treating a medical condition responsive to lamotrigine. The method includes administering a pharmaceutical composition of lamotrigine. The composition includes:

(a) from about 0.1% to about 50% by weight of lamotrigine or acid addition salt thereof;

(b) from about 15.5% to about 70% by weight of microcrystalline cellulose;

(c) from about 0.1% to about 14.5% by weight of sodium starch glycolate; and

(d) from about 0.1% to about 4.5% by weight of polyvinylpyrrolidone.

Embodiments of the method may include one or more of the following features or those described above. For example, the pharmaceutical composition may further include from about 0.1% to about 14.5% by weight of lactose.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Description of the Invention

In seeking to develop a stable pharmaceutical composition of lamotrigine, the inventors have developed several dosage forms and processes for their preparation. The inventors have found that a stable tablet of lamotrigine can be prepared by wet granulation with about 15.5% to about 70% by weight of microcrystalline cellulose, about 0.1% to about 14.5% by weight of sodium starch glycolate, and about 0.1% to about 4.5% by weight of polyvinylpyrrolidone, with or without the inclusion of lactose.

As used herein lamotrigine refers to its free base or acid addition salt, such as, methanesulphonate and isothionate salts. For example, formulations may include from about 0.1% to about 50% by weight of lamotrigine or a lamotrigine salt by weight of the tablet.

Microcrystalline cellulose is commonly used as a filler in tablets. It is a white, odorless, tasteless, free flowing powder. There are various grades available which differ in bulk density, particle size and moisture content. Particularly suitable fillers include one or more of Avicel PH101, Avicel PH102, Tabulose®101, Tabulose®102, Vivapur®102 or a combination thereof. These grades have a particle size in the range of about 50μ to about 100μ. The microcrystalline cellulose may be present in the tablet in an amount of from about 15.5% to about 70% by weight of the tablet, more particularly from about 17% to about 70% by weight of the tablet, and even more particularly from about 20% to about 70% by weight of the tablet.

Sodium starch glycolate is used herein as a disintegrant. It is a white to off-white, tasteless, odorless, relatively free flowing powder. Sodium starch glycolate absorbs water rapidly, resulting in swelling, which leads to rapid disintegration of tablets and granules that include the sodium starch glycolate. It can be used intragranularly as well as extragranularly and may be present in amounts of from about 0.1% to about 14.5% by weight of the tablet, more particularly from about 0.1% to about 13% by weight of the tablet, and even more particularly from about 0.1% to about 10% by weight of the tablet.

Polyvinylpyrrolidone is a commonly used binder. It is a white or creamy white powder and is available at different molecular weights. Suitable grades include those having molecular weights of from about 40,000 to 1,300,000 Daltons. Povidone K30 and Povidone K90 and combinations thereof are particularly suitable. Polyvinylpyrrolidone may be present in an amount of from about 0.1% to about 4.5% by weight of the tablet, more particularly from about 0.1% to about 4% by weight of the tablet, and even more particularly from about 0.1% to about 3% by weight of the tablet.

Lactose is another commonly used filler in tablets. It is a white or almost white, free flowing powder. Lactose may include anhydrous lactose, such as Pharmatose® grades 150M, 200M, 350M, 450M, DCL21 and combinations thereof. Lactose may be present in an amount of from about 0.1% to about 14.5% by weight of tablet, in particular from about 0.1% to about 13% by weight of the tablet, and, more particularly, from about 0.1% to about 10% by weight of the tablet.

The present pharmaceutical composition may also include one or more glidants and lubricants, such as talc, colloidal silicon dioxide, magnesium stearate and sodium stearyl fumarate. Generally, these may be present in an amount of from about 0.1% to about 2% weight by weight of the tablet.

A pharmaceutical composition was prepared by wet granulation. Lamotrigine or its acid addition salt was mixed with microcrystalline cellulose, sodium starch glycolate, lactose, and polyvinylpyrrolidone. The blend was then granulated with purified water in a rapid mixer granulator. Alternatively, a blend including lamotrigine or its acid addition salt, microcrystalline cellulose, sodium starch glycolate and lactose may be granulated with an aqueous solution of polyvinylpyrrolidone. The wet mass was then screened to obtain granules. The granules were dried and mixed with extragranular excipients such as fillers (e.g., microcrystalline cellulose), disintegrants (e.g., sodium starch glycolate), lubricants (e.g., magnesium stearate) and glidants (e.g., talc and colloidal silicon dioxide). The resulting mixtures were then compressed into tablets using appropriate tooling.

The phrase 'stable formulation' herein refers to a formulation of lamotrigine in which there is no change in assay values, impurity percentages and dissolution data when kept at 40°C/75% RH for 3 months. Lamotrigine raw material and tablets have been reported to have two impurities (A) 3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-5-(4H)-one; and (B) N-(5-amino-6-(2,3-dichloropneyl)-1,2,4-triazine-3-yl)-2,3-dichlorobenzamide (B). The impurity A is a degradation product produced during the hydrolysis of lamotrigine and impurity B is a process impurity formed during the synthesis of lamotrigine.

In the tablets prepared by the processes described herein, the degradation products are either not formed or are below the level of quantification.

The following examples illustrate stable pharmaceutical compositions of lamotrigine and processes of making the compositions as disclosed in the various embodiments discussed throughout the specification. The examples are merely provided to illustrate the compositions and processes for their preparation and are not intended to be limiting. The obvious variations of these compositions are contemplated to be within the scope of the present invention and the appended claims.

EXAMPLE 1

Ingredients	Quantity (mg)
Intragranular	
Lamotrigine	200
Lactose	25
Microcrystalline cellulose	40.5
Sodium Starch Glycolate	16
Polyvinylpyrrolidone	15
Iron oxide (yellow)	0.5
Purified water	q.s
Extragranular	
Microcrystalline cellulose	71
Sodium starch glycolate	24
Magnesium stearate	4
Talc	2
Colloidal silicon dioxide	2
Total	**400**

METHOD:

The tablets of Example 1 were prepared as follows:

1. Lamotrigine, lactose, polyvinylpyrrolidone, iron oxide (yellow), a portion of microcrystalline cellulose (i.e., the intragranular portion), and a portion of sodium starch glycolate (i.e., the extragranular portion) were sifted through a suitable mesh and mixed for 10 minutes.
2. The blend of Step 1 was granulated with purified water.
3. The granules were dried in a fluid bed dryer.
4. Colloidal silicon dioxide and the remaining portion of microcrystalline cellulose (i.e., the extragranular portion) and the remaining portion of sodium starch glycolate (i.e., the extragranular portion) were sifted through a suitable mesh and mixed with the dried

granules of step 3.

5. Talc and magnesium stearate were then mixed with the blend of step 4 and compressed using a suitable punch tooling to form tablets.

The tablets of Example 1 were subjected to accelerated studies for three months at 40°C and 75% relative humidity (RH) and the results are shown in Table 1.

Table 1: Stability data of lamotrigine tablets prepared as per Example 1 and subjected to accelerated studies.

	Initial	3 Months/40°C/75%RH
Lamotrigine (% w/w)	100.15	99.82
Impurity A (% w/w)	ND*	BLQ**
Total related substances (%w/w)	0.046	0.053

*Not Detected

** Below level of quantification

The tablets of Example 1 were also subjected to dissolution studies in USP 2 apparatus at 50 RPM in 900 mL of 0.1N HCl. The dissolution profile of the tablets at the initial and 3 months period is given in Table 2.

Table 2: Dissolution profile of tablets prepared as per the composition of Example 1 (in USP 2 apparatus at 50 RPM in 900 mL of 0.1N HCl).

Time (min)	% Release	
	Initial	3 months/40°C/75%RH
10	89	90
20	97	99
30	100	101
45	100	104

As evident from the data reported in Table 3, the tablets of Example 1 release the entire drug content within thirty minutes.

EXAMPLE 2

Ingredients	Quantity (mg)
Intragranular	
Lamotrigine	5
Lactose	5.75
Microcrystalline cellulose	15.6
Sodium Starch Glycolate	2.5
Polyvinylpyrrolidone	1.875
Iron oxide (yellow)	0.625
Purified water	q.s
Extragranular	
Microcrystalline cellulose	14.65
Sodium starch glycolate	2.5
Magnesium stearate	0.5
Talc	0.5
Colloidal silicon dioxide	0.5
Total	**50**

METHOD:

The tablets of Example 2 containing lamotrigine (5 mg) were prepared as described above with respect to the process of Example 1. In Example 2, the microcrystalline cellulose is present at about 60% by weight of tablet.

EXAMPLE 3

Ingredients	Quantity (mg)
Intragranular	
Lamotrigine	200
Microcrystalline Cellulose	156
Sodium Starch Glycolate	5
Polyvinylpyrrolidone	20
Purified Water	q.s
Extragranular	
Sodium Starch Glycolate	15
Magnesium Stearate	2
Colloidal Silicon Dioxide	2
Total	**400**

METHOD:

The tablets of Example 3 containing lamotrigine (5 mg) were prepared as described above with respect to the process of Examples 1 and 2, although without lactose being present. The tablets of Example 3 were subjected to accelerated studies for three months at 40°C and 75% relative humidity. The results of these studies are reported in Table 3.

Table 3: Stability data of lamotrigine tablets prepared as per Example 3 and subjected to accelerated studies.

	Initial	3 Months/40°C/75%RH
Lamotrigine (% w/w)	99.67	99.43
Impurity A (% w/w)	ND*	BLQ**
Total related substances (%w/w)	0.043	0.054

*Not Detected ** Below level of quantification

The dissolution profile of the tablets of Example 3 were measured in USP 2 apparatus at 50 RPM in 900 mL of 0.1N HCl. The dissolution profile of the tablets at the initial and 3 months period is reported in Table 4.

Table 4: Dissolution profile of tablets prepared as per the composition of Example 3 (in USP 2 apparatus at 50 RPM in 900 mL of 0.1N HCl).

Time (min)	% Release	
	Initial	3 months/40°C/75%RH
10	88	81
20	97	97
30	100	92
45	101	102

As evident from the data reported in Table 4, the tablets of Example 3 release the entire drug content within forty-five minutes.

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations in the preferred methods of the present invention may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.